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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,125	PIZZA ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11 and 14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Non-Final Office Action dated 08/04/09, applicants' response and claim amendments filed on 02/01/10 is acknowledged, said response amended claims 1-7, 9, 11 and 14.

Amended claims 1-7, 9, 11 and 14 are pending, claim 14 remains withdrawn as said claim is directed to nonelected invention, thus amended claims 1-7, 9 and 11 are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn-Claim Rejections: 35 USC § 112

Previous rejection of claims 1-3 and 11 under 35 U.S.C. 112, second paragraph is withdrawn due to claim amendments.

New-Claim Objections

Claims 1 and 5 are objected for the recitation of "…80% identity to SEQ ID NO: 1…", the metes and bounds of the claim are not clear, said percent identity does not distinguish between structure and function, as there is no function associated with the claims, examiner suggests amending the clams to recite "…80% sequence identity to SEQ ID NO: 1…",

Claim 2 is objected for the recitation of "and/or" in the claims, examiner suggests amending the claim to read "…or…" Correction is required.

Maintained-Double Patenting rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d

887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 38, 45 and 46 of Masignani et al., (US Application No.: 10/472,681). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claims are not patentably distinct from the reference claims, because the examined claims are either anticipated by, or would have been obvious over reference claims. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-7, 9 and 11 of the instant application are directed to any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims

5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11). Claims 27, 28, 36, 38, 45 and 46 of the reference application Masignani et al., (US Application No.: 10/472,681) are also directed to an isolated adenosine diphosphate (ADP)-ribosylating protein comprising an amino acid sequence having greater than 80%-95% sequence identity to the amino acid sequence of SEQ ID NO: 1 (the SEQ ID NO: 1 of the reference application has 100% sequence homology to SEQ ID NO: 1 of the instant application), wherein the ADP-ribosylating activity of the polypeptide is reduced or eliminated as compared to the wild-type sequence of SEQ ID NO: 1 (as in claims 27, 45 and 46 of the reference application), said polypeptide further comprising one or more mutations selected from the group of mutations (as in claim 28 of the reference application) such as Glu 109 mutated to Asp (as in SEQ ID NO: 2 of the instant application, claim 4), Glu 111 mutated to Asp (as in SEQ ID NO: 3 of the instant application, claim 4), Glu 120 mutated to Asp (as in SEQ ID NO: 4 of the instant application, claim 4) and immunogenic compositions comprising the said polypeptide and an antigen (as in claims 36 and 38 of the reference application). The copending claims therefore encompass a genus of polypeptides, which overlaps with the genus of instant claims i.e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein

comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11), as recited in claims 1-7, 9 and 11 of the instant application cannot be considered patentably distinct over 27, 28, 36, 38, 45 and 46 of reference application Masignani et al., (US Application No.: 10/472,681), when there is specifically recited embodiment in the copending application which supports the claimed genus, that would anticipate claims 1-7, 9 and 11 of the instant application. Alternatively, claims 1-7, 9 and 11 of the instant application cannot be considered patentably distinct over claims 27, 28, 36, 38, 45 and 46 of reference application Masignani et al., (US Application No.: 10/472,681) when there is specifically disclosed embodiment in the reference application of Masignani et al., (US Application No.: 10/472,681) that supports claims 27, 28, 36, 38, 45 and 46 of that application and falls within the scope of the claims 1-7, 9 and 11 herein i. e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims

5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11), because it would have been obvious to one having ordinary skill in the art to modify claims 27, 28, 36, 38, 45 and 46 of the reference by selecting a specifically disclosed embodiment that supports those claims of the copending application. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being preferred embodiment within claims 27, 28, 36, 38, 45 and 46 of the reference application of Masignani et al., (US Application No.: 10/472,681).

In response to the above rejection applicants' provide the following argument:

"Applicants respectfully request that the examiner hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter. Only at that time will the applicants be able to determine whether an obviousness-type double patenting rejection is applicable..." **(page 4 of applicants' response dated 02/01/10**).

Reply: None of the claims are ready to be allowed and therefore the above rejection is maintained.

Maintained-Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Maintained-Enablement

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mutant *Neisseria*

meningitides ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), does not reasonably provide enablement for any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, **to use** the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 5-7, 9 and 11 are so broad as to encompass for any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this case the disclosure is limited to an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO:

1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claims, i.e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11), the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill **how to use** the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in

any protein and the result of such modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11). The specification does not enable the full scope of claims 1-3, 5-7, 9 and 11, because the specification does not establish: **(A)** any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes

any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7), the structure of all polypeptides with desired activity i.e., reduced or eliminated ADP-ribosyltransferase activity and as an immunogen; **(B)** the general tolerance of the polypeptide to modification and extent of such tolerance; **(C)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(D)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides and encoding polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims

5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11), is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that said rejection be withdrawn, applicants' provide the following common arguments for both enablement and written description*: *(pages 5 and 6 of applicants' response dated 02/01/10).

"Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, applicants have amended claim 1 to remove the recitation mutant Neisseria meningitides ADP-ribosylating enzyme".

Reply: Applicants' arguments filed on **02/01/10** have been fully considered but they are not persuasive and examiner continues to maintain the rejection for reasons stated on record. The scope of these claims are broad despite the guidance of the art and specification, the claims remain not commensurate in scope with the enabled invention. Examiner finds support for his position in the following scientific teachings:

1) The specification and art describes the structure of a single *Neisseria meningitides* ADP-ribosylating enzyme. However, there is yet a possibility that many other unknown alleles in many different strains of *Neisseria meningitides* that have similar or identical functions as ADP-ribosylating enzyme like and exhibiting a highly conserved catalytic domain that serves as the NAD-binding cavity with unique molecular

signature, said signatures not corresponding to Glu-109, Glu-111 or Glu-120 could be potentially discovered and described. Thus, structure correlating to function is required if specific codon positions are recited in the claims to enable a skilled artisan to understand which specific structure is being referred to in the claims, and as such, the recitation of specific positions without a sequence identifier associated to those positions is unclear and confusing, because the codon recited may well be different from the one applicants intend to encompass.

2) The art teaches several examples annotated as ADP-ribosylating enzyme with disparate structures (see enclosed printout from PubMed, 340 structures are known), i.e., lack of primary structure homology (Domenighini et al., Mol. Microbiol., 1994, Vol. 14 (1): 41-50, in IDS). In parallel, the art also teaches, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β̃-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have

same function but different structures. It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a β̃-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β̃-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

Given this scenario, a skilled artisan needs to be provided with the structure associated with the function. Therefore, examiner would like to point out that none of the claims as written recite any limitation regarding structure with the associated function and only claim 2 recites reduced or eliminated catalytic activity and therefore examiner continues to hold the position that applicants' have construed that the amendments to claims limits the claims only to what is disclosed in the specification and the crux of the applicants' argument is based on this conception i. e., the mutation encompasses only the catalytic residues of Glu-109, Glu-111 or Glu-120 of SEQ ID NO: 1. However, examiner would like to reiterate that the conception/belief of the applicant is not correct. Amended claims as written when given the broadest reasonable interpretation reads on any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said

polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11).

Furthermore, the specification only discloses three specific mutants (SEQ ID NO: 2, 3 & 4) comprising the full-length sequence of SEQ ID NO: 1 having reduced or eliminated ADP ribosyltransferase and or NAD-glycohydrolase activity as compared to the wild-type enzyme and said mutants to be immunogenic. However, the specification has not provided structure-function correlationship (reduced catalytic activity or increased immunogenecity or able to elicit protective antibodies) i. e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in

claim 11). Therefore, the specification does not provide support for the full scope and breadth of the claims even following the amendments to claims and examiner continues to hold the position the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue.

Therefore, examiner takes the position that due to the paucity of information regarding structure-function correlation, the specification lacks identifying characteristics of all of the sequences within the claimed genus, especially; any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11) and would clearly constitute **undue** experimentation.

Maintained-Written Description

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-7, 9 and 11, as interpreted, are directed to a genus of polypeptides i.e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11).

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no structure-function correlation (undefined biological or structural or chemical or functional elements/features are encompassed, also see claim objections) recited in claims with regard to the members of the genus

polypeptides i.e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11).

While the specification in the instant application discloses the structure; an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), it fails to provide any information as to the structure-function correlationship for the genus of polypeptides claimed i.e., any polypeptide of undefined function having at least 80% identity to SEQ ID NO: 1, wherein said polypeptide has a substitution at one or more amino acids corresponding to Glu-109 or Glu-111 or Glu-120 of SEQ ID NO: 1 (as in claims 1 and 3) or said polypeptide has reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity relative to SEQ ID NO: 1 (as in claims 2 and 3) or any protein comprising a fragment of undefined structure of a polypeptide having at

least 80% identity to SEQ ID NO: 1 that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 (as in claims 5, 6 and 9) or said polypeptide comprises at least 7 consecutive amino acids of said polypeptide (as in claim 7) and use of said polypeptide as an immunogen (as in claim 11). The lack of description of any additional mutants and use of said mutant as an immunogen by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that said rejection be withdrawn, applicants' provide the following common arguments for both enablement and written description*: *(pages 5 and 6 of applicants' response dated 02/01/10).

"Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, applicants have amended claim 1 to remove the recitation mutant Neisseria meningitides ADP-ribosylating enzyme".

Reply: Applicants' arguments filed on **02/01/10** have been fully considered but they are not persuasive and examiner continues to maintain the rejection for reasons stated on record, supporting evidence and arguments presented in maintaining the enablement rejection above.

In addition, the genus of polypeptides required in the claimed invention is an extremely large structurally and functionally variable genus with no structure-function correlation. While the argument can be made that the recited genus of polypeptides is adequately described by the disclosure of the structure of a protein comprising the amino acid sequence of SEQ ID NO: 1 or mutants/variants of SEQ ID NO: 1: SEQ ID NO: 2 or SEQ ID NO: 3 or SEQ ID NO: 4 having ADP ribosyltransferase or NAD-glycohydrolase activity, since one could use structural homology to isolate those polypeptides recited in the claims. The art clearly teaches the "Practical Limits of Function Prediction": **I.** Devos et al., (Proteins: Structure, Function and Genetics, 2000, Vol. 41: 98-107), teach that the results obtained by analyzing a significant number of true sequence similarities, derived directly from structural alignments, point to the complexity of function prediction. Different aspects of protein function, including (i) enzymatic function classification, (ii) functional annotations in the form of key words, (iii) classes of cellular function, and (iv) conservation of binding sites can only be reliably transferred between similar sequences to a modest degree. The reason for this difficulty is a combination of the unavoidable database inaccuracies and plasticity of proteins (Abstract, page 98) and the analysis poses interesting questions about the reliability of current function prediction exercises and the intrinsic limitation of protein function prediction (Column 1, paragraph 3, page 99) and conclude that "Despite widespread use of database searching techniques followed by function inference as standard procedures in Bioinformatics, the results presented here illustrate that transfer of function between similar sequences involves more difficulties than commonly believed.

Our data show that even true pair-wise sequence relations, identified by their structural similarity, correspond in many cases to different functions (column 2, paragraph 2, page 105).

II. Whisstock et al., (Quarterly Reviews of Biophysics 2003, Vol. 36 (3): 307-340, in IDS) also highlight the difficulties associated with "Prediction of protein function from protein sequence and structure"; "To reason from sequence and structure to function is to step onto much shakier ground", closely related proteins can change function, either through divergence to a related function or by recruitment for a very different function, in such cases, assignment of function on the basis of homology, in the absence of direct experimental evidence, will give the wrong answer (page 309, paragraph 4), it is difficult to state criteria for successful prediction of function, since function is in principle a fuzzy concept. Given three sequences, it is possible to decide which of the three possible pairs is most closely related. Given three structures, methods are also available to measure and compare similarity of the pairs. However, in many cases, given three protein functions, it would be more difficult to choose the pair with most similar function, although it is possible to define metrics for quantitative comparisons of different protein sequences and structures, this is more difficult for proteins of different functions (page 312, paragraph 5), in families of closely related proteins, mutations usually conserve function but modulate specificity i.e., mutations tend to leave the backbone conformation of the pocket unchanged but to affect the shape and charge of its lining, altering specificity (page 313, paragraph 4), although the hope is that highly similar proteins will share similar functions, substitutions of a single, critically placed amino acid

in an active-site residue may be sufficient to alter a protein's role fundamentally (page 323, paragraph 1).

III. This finding is reinforced in the following scientific teachings for specific proteins in the art that suggest, even highly structurally homologous polynucleotides and encoded polypeptides do not necessarily share the same function. For example, Witkowski et al., (Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β̃-ketoacyl synthase activity. Seffernick et al., (J. Bacteriol. 183(8): 2405-2410, 2001), teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase.

As stated above, no information beyond the characterization of a <u>few species</u>: a wild-type parent ADP ribosyltransferase of SEQ ID NO: 1 and a specific variants of SEQ ID NO: 2 or SEQ ID NO: 3 or SEQ ID NO: 4, has been provided by the applicants', which would indicate that they had possession of the claimed genus of polypeptides. As the claimed genera of polypeptides having widely variable structure and associated function, since minor changes in structure may result in changes affecting function and no additional information (species/variant/mutant) correlating structure with function has been provided. Furthermore, <u>"Possession may not be shown by merely describing how</u>

to obtain possession of members of the claimed genus or how to identify their common structural features" (See *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895).

Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 1-7, 9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 38, 45 and 46 of Masignani et al., (US Application No.: 10/472,681).

2) Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, for enablement and written description.

Conclusion

None of the claims are allowable. Claims 1-7, 9 and 11 are rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in

this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652